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Description

This invention relates to novel compounds which are useful in treating or preventing diseases characterized by abnormal calcium and phosphate metabolism, in particular those which are characterized by abnormal bone metabolism. This invention further relates to pharmaceutical compositions which contain the novel compounds of the present invention.

A number of pathological conditions which can afflict warm-blooded animals involve abnormal calcium and phosphate metabolism. Such conditions may be divided into two broad categories.

1. Conditions which are characterized by anomalous mobilization of calcium and phosphate leading to general or specific bone loss, or excessively high calcium and phosphate levels in the fluids of the body. Such conditions are sometimes referred to herein as pathological hard tissue demineralizations.
2. Conditions which cause or result from deposition of calcium and phosphate anomalously in the body. These conditions are sometimes referred to herein as pathological calcifications.

The first category includes osteoporosis, a condition in which bone hard tissue is lost disproportionately to the development of new hard tissue. Marrow and bone spaces become larger, fibrous binding decreases, and compact bone becomes fragile. Osteoporosis can be subclassified as menopausal, senile, drug induced (e.g., adrenocorticoid, as can occur in steroid therapy), disease-induced (e.g., arthritic and tumor), etc., however, the manifestations are essentially the same. Another condition in the first category is Paget's disease (osteitis deformans). In this disease, dissolution of normal bone occurs which is then haphazardly replaced by soft, poorly mineralized tissue such that the bone becomes deformed from pressures of weight bearing, particularly in the tibia and femur. Hyperparathyroidism, hypercalcemia of malignancy, and osteolytic bone metastases are conditions also included in the first category.

The second category, involving conditions manifested by anomalous calcium and phosphate deposition, includes myositis ossificans progressiva, calcinosis universalis, and such afflictions as arthritis, neuritis, bursitis, tendonitis and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphates.

Polyphosphonic acids and their pharmaceutically-acceptable salts have been proposed for use in the treatment and prophylaxis of such conditions. In particular, diphosphonates like ethane-1-hydroxy-1 ,1-diphosphonic acid (EHDP) , propane-3-amino-1-hydroxy-1,1-diphosphonic acid (APD), and dichloromethane diphosphonic acid (Cl_2MDP) have been the subject of considerable research efforts in this area. Paget's disease and heterotopic ossification are currently successfully treated with EHDP. The diphosphonates tend to inhibit the resorption of bone tissue, which is beneficial to patients suffering from excessive bone loss. However, EHDP, APD and many other prior art diphosphonates have the propensity of inhibiting bone mineralization when administered at high dosage levels.

It is therefore an object of this invention to provide novel diphosphonate compounds which inhibit the resorption of bone tissue and have a reduced propensity of inhibiting bone mineralization. It is a further object of this invention to provide compositions for the treatment and prophylaxis of abnormal calcium and phosphate metabolism.

The preparation of the tetraethyl ester of xanthane-9,9-diphosphonic acid is disclosed in Mustafa et al., Ann., 698, 109 (1966). The synthesis of the diphosphonomethylene ether of 1,2 dihydroxybenzene is disclosed in Gross et al., Liebigs Ann. Chem., 707, 35 (1967). Neither reference discloses a specific utility for the compounds described therein.

US-A-3,683,080, issued August 8, 1972 to Francis, discloses compositions comprising polyphosphonates, in particular diphosphonates, and their use in inhibiting anomalous deposition and mobilization of calcium phosphate in animal tissue.

US-A-4,330,537, issued October 28, 1980 to Francis, discloses compositions comprising certain phosphonate compounds in combination with vitamin D-like compounds for use in inhibiting mobilization of calcium phosphate in animal tissue. Among the phosphonate compounds disclosed therein are cycloalkyl - substituted hydroxymethane diphosphonates and vicinal diphosphonates of fluorinated cycloalkenes.

US-A-3,988,433, issued October 26, 1976 to Ploger et al., discloses azacycloalkane-2,2-diphosphonic acids. The compounds are said to be useful as sequestering agents, as stabilizers for percompounds, in delaying the setting of gypsum, in preventing the formation of tartar and plaque, and in the treatment of diseases related to the abnormal deposition or dissolution of difficultly soluble calcium salts in the animal body.

The present invention relates to a geminal cycloalkyl diphosphonic acid or a pharmaceutically-acceptable salt thereof selected from:

(a) substituted or unsubstituted dihydro-1-pyrindine-6,6-diphosphonic acids; and

(b) substituted or unsubstituted dihydro-2-pyrindine-6,6-diphosphonic acids;

wherein the substituents of said substituted cycloalkyl diphosphonic acid are selected from methyl, methylamino, amino, chloro, hydroxy and methoxy.

The invention further encompasses pharmaceutical compositions comprising a diphosphonic acid compound of this invention, and a pharmaceutical carrier.

By "pharmaceutically-acceptable salts and esters" as used herein is meant salts of the diphosphonate compounds which have the same general pharmacological properties as the acid form from which they are derived, and which are acceptable from a toxicity viewpoint. Pharmaceutically-acceptable salts include alkali metal (sodium and potassium), alkaline earth metal (calcium and magnesium), non-toxic heavy metal (stannous and indium), and ammonium and low molecular weight substituted ammonium (mono-, di- and triethanolamine) salts. Preferred compounds are the sodium, potassium, and ammonium salts.

The compounds of the present invention are useful in the treatment of conditions in humans and animals characterized by abnormal calcium and phosphate metabolism. Other diphosphonates have been suggested for such use, in particular ethane-1-hydroxy-1,1-diphosphonate (EHDP), propane-3-amino-1-hydroxy-1,1-diphosphonate (APD), and dichloromethane diphosphonic acid (Cl_2MDP).

Although metabolic bone disorders have successfully been treated with the above art-disclosed diphosphonates, EHDP and APD have the tendency to inhibit bone mineralization as well as bone resorption. Administration of these compounds must therefore be carefully monitored in order to maximize bone resorption inhibition while avoiding inhibition of bone mineralization.

It has been discovered that in vitro cyclic diphosphonates generally have a much reduced potency for bone mineralization inhibition when compared to EHDP and APD. It has also been discovered that certain cyclic diphosphonates in vivo inhibit the resorption of bone tissue. Thus, at equally effective doses for inhibition of bone resorption, the compounds of the present invention are expected to inhibit bone mineralization to a lesser extent than many art-disclosed diphosphonates. The compounds of this invention therefore allow flexibility in the treatment of patients suffering from abnormal calcium and phosphate metabolism. The compounds of the present invention are also useful as bone scanning agents after labeling with 99m-Technetium.

The compounds of the present invention are also useful as sequestering agents for polyvalent metal ions, particularly di- and tri-valent metal ions, and therefore may be used for many technical applications, such as builders in detergents and cleansers, as well as in water treatment. They also may be used as stabilizers for percompounds. Other uses for the diphosphonic acids of the present invention are apparent to one skilled in the art.

Specific examples of compounds of the present invention include: dihydro-1-pyrindine-6,6-diphosphonic acid; 2-chloro-dihydro-1-pyrindine-6,6-diphosphonic acid; 4-methoxy-dihydro-1-pyrindine-6,6-diphosphonic acid; 5-amino-dihydro-1-pyrindine-6,6-diphosphonic acid; dihydro-2-pyrindine-6,6-diphosphonic acid; 4-chlorodihydro-2-pyrindine-6,6-diphosphonic acid; 7-methyl-dihydro-2-pyrindine-6,6-diphosphonic acid; 1-(aminomethyl)-dihydro-2-pyrindine-6,6-diphosphonic acid; and pharmaceutically-acceptable salts thereof.

Crystal Growth Inhibition Test

The relative affinity of cyclic diphosphonates for calcified tissues is demonstrated by the crystal growth inhibition test. This test was developed for polyphosphonates to establish their potential to reduce calcium phosphate deposition and has been shown to be predictive of the affinity of these compounds for calcified tissues like bone. The test is described in detail by Nancollas, et al., Oral Biol., 15, 731 (1970).

In this test, hydroxyapatite seed crystals are added to a calcium/phosphate solution supersaturated with respect to induced precipitation of calcium phosphates but meta-stable toward spontaneous precipitation. The seed crystals induce precipitation and crystal growth. Test chemicals are added to the meta-stable Ca/P solution before seeding. The effect of these chemicals on formation of hydroxyapatite induced by seed crystals has been shown to correlate with in vivo effects of these chemicals on calcium metabolism.

Formation of calcium phosphate crystals results in the release of hydrogen ions (i.e., pH change). The rate of crystal growth is monitored by observing the addition of base required to maintain a constant pH. Low levels (1×10^{-6} M) of polyphosphonates are capable of inhibiting the formation of calcium phosphate for 20 minutes or longer. Crystal growth inhibition depends on the propensity of the polyphosphonates to adsorb on calcium phosphate crystal nuclei.

In the test, the time lapse, T, between addition of seed crystal and the start of crystal growth is measured. The effect of the presence of a diphosphonate compound is calculated as

$$T_{lag} = T_{DP} - T_{contr}$$

wherein T_{DP} is the time lapse for the experiment with 1×10^{-6} M of the diphosphonate compound present in the test solution, T_{contr} is the time lapse in the experiment without diphosphonate, and T_{lag} is the lag time resulting from the presence of the diphosphonate in the solution. For the present purpose, the lag times have been normalized (T_n; where T_n (EHDP) = 1.0), by dividing the lag time for each compound by that measured for EHDP (T_n = T_{lag} (test compound)/T_{lag} (EHDP)). The T_n values for various compounds are provided in Table 1.

It has been discovered that diphosphonates which possess low T_{lag} values relative to EHDP in this test have a relatively low propensity for in vivo bone mineralization inhibition.

Table I

Mineralization Inhibition (Crystal Growth Inhibition Test)	
Diphosphonate Compound	T_n
EHDP [1)]	1.0
APD [2)]	0.9
Cl_2MDP [3)]	0.1
Dihydro-1-pyrindine-6,6-DP *	0.3

*= Compound useful in the pharmaceutical compositions of the present invention

[1)] Ethane-1-hydroxy-1,1-DP

[2)] 3-Aminopropane-1-hydroxy-1,1-DP

[3)] Dichloromethane-DP

SYNTHESIS OF CYCLIC DIPHOSPHONATE COMPOUNDS

The synthesis reaction is carried out in the following way: In a first step, a methane diphosphonate ester, in solution, is converted to the corresponding carbanion using standard organic chemistry techniques. In a second step, to this reaction mixture is added a solution of a hydrocarbon compound suitably activated for a double nucleophilic substitution.

Typically, a solution of methane diphosphonate ester will be added to a cold suspension of potassium hydride in an inert organic solvent, and the solution left to stir at room temperature for a while. The suitably activated hydrocarbon will next be added as a solution to the reaction mixture, and the entire mixture then be heated to about 80 °C until completion. After the mixture has been cooled, filtered, and concentrated, the concentrate is chromatographed on silica gel to obtain the desired ester. The ester is hydrolyzed by refluxing in HCl and the resulting material concentrated under vacuum. The residue is dissolved in H_2O and treated with activated charcoal. Following filtration, the solution is concentrated, and the product is finally dried under vacuum. Synthesis of salts and esters of these compounds is achieved using standard organic chemistry techniques well-known to those skilled in the art.

Following are examples of the synthesis of specific cyclic diphosphonates of this invention. The compounds were identified by ^{1}H NMR using Me_4Si or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standards, and by ^{31}P NMR using H_3PO_4 as an external standard (positive values denote a chemical shift downfield from the reference); by chemical ionization mass spectrometry; by melting point determination; and by elemental analysis.

EXAMPLE I

Synthesis of Dihydro-1-pyrindine-6,6-diphosphonic acid

To an ice bath chilled solution of 35% potassium hydride in mineral oil (5.2g 0.045 moles) stirring under argon in 70 ml of DMSO (dry) was added a solution of tetraisopropylmethanediphosphonate (7.82g, 0.023 moles) in 30 ml of DMSO. On completion of a dropwise addition the resulting solution was stirred at room temperature for one hour. A solution of 2,3-bis(chloromethyl)pyridine (4.0g, 0.023 mole) (crude product as isolated by K. Tsuda et.al. Chem Pharm Bull 1, (1953) 142) in 15 ml of DMSO was slowly added and the reaction mixture was then heated at 90 °C for 1 hour. After cooling the DMSO was removed under vacuum. 2.1g (21%) of the desired product was purified via flash chromatography using a 5-15% ethanol in

methylene chloride gradient on silica gel. The resulting tan oil gave the following spectral characteristics: ^1H NMR ($CDCl_3$) 8.34 (d, 1H), 7.45 (d, 1H), 7.02 (dd, 1H), 4.77 (m, 4H), 3.58 (dt, 4H), 1.35 (d, 24 H); ^{31}P NMR ($CDCl_3$) 23.97 ppm (s).

The ester (1.92 g, 0.0043 mole) was added to 38 ml of 6N HCl, and then refluxed with stirring under an argon atmosphere for 18 hours. The resulting precipitate was filtered, rinsed with water (2 x 5 ml), and dried to yield 0.8 g (66.5%) of an off-white crystalline solid: mp > 300° C (dec); ^1H NMR (D_2O/NaOD) 8.19 (d, 1H, J = 3.4 Hz), 7.62 (d, 1H, J = 7.5 Hz), 7.13 (dd, 1H, J=3.4 and 7.5 Hz), 3.46 (t, 4H, J = 15.8 Hz); ^{31}P NMR (D_2O/NaOD) 24.84 ppm (s).

EXAMPLE II

Synthesis of Dihydro-2-pyrindine-6,6-diphosphonic acid

Using the same procedure as in Example I, tetraisopropyl methane diphosphonate is converted to tetraisopropyl dihydro-2-pyrindine-6,6-diphosphonate by reaction with 3,4-bis(chloromethyl)pyridine. The resulting ester is hydrolyzed as in Example I to yield the dihydro-2-pyrindine-6,6-diphosphonic acid.

The compositions of the invention are used for treating or preventing diseases characterized by abnormal calcium and phosphate metabolism, in particular those which are characterized by abnormal bone metabolism, in persons at risk to such disease. The preferred mode of administration is orally, but other modes of administration include, without limitation, transdermal, mucosal, sublingual, intramuscular, intravenous, intraperitoneal, and subcutaneous administration, as well as topical application.

By "abnormal calcium and phosphate metabolism" as used herein is meant (1) conditions which are characterized by anomalous mobilization of calcium and phosphate leading to general or specific bone loss, or excessively high calcium and phosphate levels in the fluids of the body; and (2) conditions which cause or result from deposition of calcium and phosphate anomalously in the body. The first category includes, but is not limited to, osteoporosis, Paget's disease, hyperparathyroidism, hypercalcemia of malignancy, and osteolytic bone metastases. The second category includes, but is not limited to, myositis ossificans progressiva, calcinosis universalis, and such afflictions as arthritis, neuritis, bursitis, tendonitis and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphates.

By "person at risk", or "person in need of such treatment", as used herein is meant any human or lower animal which suffers a significant risk of abnormal calcium and phosphate metabolism if left untreated, and any human or lower animal diagnosed as being afflicted with abnormal calcium and phosphate metabolism. For example, postmenopausal women; persons undergoing certain steroid therapy; persons on certain anti-convulsant drugs; persons diagnosed as having Paget's disease, hyperparathyroidism, hypercalcemia of malignancy, or osteolytic bone metastases; persons diagnosed as suffering from one or more of the various forms of osteoporosis; persons belonging to a population group known to have a significantly higher than average chance of developing osteoporosis, e.g., postmenopausal women, men over age 65, and persons being treated with drugs known to cause osteoporosis as a side effect; persons diagnosed as suffering from myositis ossificans progressiva or calcinosis universalis; and persons afflicted with arthritis, neuritis, bursitis, tendonitis and other inflammatory conditions which predispose involved tissue to deposition of calcium phosphate.

By "human or lower animal afflicted with or at risk to osteoporosis" as used herein is meant a subject diagnosed as suffering from one or more of the various forms of osteoporosis, or a subject belonging to a group known to have a significantly higher than average chance of developing osteoporosis, e.g., postmenopausal women, men over the age of 65, and persons being treated with drugs known to cause osteoporosis as a side effect (such as adrenocorticoid).

By "safe and effective amount" as used herein is meant, within the scope of sound medical judgment, an amount of a compound or composition high enough to significantly positively modify the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio). The safe and effective amount of cyclic diphosphonates of the present invention will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of treatment, the nature of concurrent therapy. and the specific diphosphonate employed. However, single dosages can range from about 0.1 mg P to about 3500 mg P, or from about 0.01 to about 500 mg P/kg of body weight. Preferred single dosages are from about 5 mg P to about 600 mg P, or from about 0.5 to about 50 mg P/kg of body weight. Up to about four single dosages per day may be administered. Daily dosages greater than about 2000 mg P/kg are not required to produce the desired effect and may produce undesirable side effects. The higher dosages within this range are, of course, required in the case of oral administration because of limited absorption.

An additional aspect of this invention is a pharmaceutical composition comprising a safe and effective amount of diphosphonate of the present invention and a pharmaceutical carrier.

By "pharmaceutical carrier" as used herein is meant one or more compatible solid or liquid filler diluents or encapsulating substances. By "compatible" as used herein is meant that the components of the composition are capable of being commingled without interacting in a manner which would substantially decrease the efficacy of the total composition under ordinary use situations.

Some examples of the substances which can serve as pharmaceutical carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethylcellulose, ethylcellulose, cellulose acetate; powdered tragacanth; malt; gelatin, talc; stearic acid; magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; agar; alginic acid; pyrogen-free water; isotonic saline; and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents and lubricants such as sodium lauryl sulfate, as well as coloring agents, flavoring agents and preservatives, can also be present. Other compatible pharmaceutical additives and actives may be included in the pharmaceutical compositions of the present invention.

The choice of a pharmaceutical carrier to be used in conjunction with the diphosphonate of the present invention is basically determined by the way the diphosphonate is to be administered. If the compound is to be injected, the preferred pharmaceutical carrier is sterile physiological saline, the pH of which has been adjusted to about 7.4. However, the preferred mode of administering the diphosphonates of the present invention is orally, and the preferred unit dosage form is therefore tablets, capsules and the like comprising from 15 mg P to 600 mg P of a diphosphonic acid compound of the present invention. Pharmaceutical carriers suitable for the preparation of unit dosage forms for oral administration are well known in the art. Their selection will depend on secondary considerations like taste, cost, shelf stability, which are not critical for the purposes of the present invention, and can be made without difficulty by a person skilled in the art. The pharmaceutical carrier employed in conjunction with the diphosphonates of the present invention is used at a concentration sufficient to provide a practical size to dosage relationship. Preferably, the pharmaceutical carrier comprises from about 0.1% to about 99.9% by weight of the total composition.

Claims

1. A geminal cycloalkyl diphosphonic acid or a pharmaceutically-acceptable salt thereof selected from:
   (a) substituted or unsubstituted dihydro-1-pyrindine-6,6-diphosphonic acids; and
   (b) substituted or unsubstituted dihydro-2-pyrindine-6,6-diphosphonic acids;
   wherein the substituents of said substituted cycloalkyl diphosphonic acid are selected from methyl, methylamino, amino, chloro, hydroxy and methoxy.

2. Dihydro-1-pyrindine-6,6-diphosphonic acid or a pharmaceutically-acceptable salt thereof.

3. Dihydro-2-pyrindine-6,6-diphosphonic acid or a pharmaceutically-acceptable salt thereof.

4. A pharmaceutical composition comprising
   a) from 15 mg P to 600 mg P of a diphosphonic acid compound of any of Claims 1 to 3; and
   b) a pharmaceutical carrier.

Patentansprüche

1. Geminale Cycloalkyldiphosphonsäure oder ein pharmazeutisch annehmbares Salz hievon, ausgewählt unter:
   (a) substituierten oder unsubstituierten Dihydro-1-pyrindin-6,6-diphosphonsäuren; und
   (b) substituierten oder unsubstituierten Dihydro-2-pyrindin-6,6-diphosphonsäuren;
   worin die Substituenten der genannten substituierten Cycloalkyldiphosphonsäure unter Methyl, Methylamino, Amino, Chlor, Hydroxy und Methoxy ausgewählt sind.

2. Dihydro-1-pyrindin-6,6-diphosphonsäure oder ein pharmazeutisch annehmbares Salz hievon.

3. Dihydro-2-pyrindin-6,6-diphosphonsäure oder ein pharmazeutisch annehmbares Salz hievon.

4. Pharmazeutische Zusammensetzung, umfassend
   a) von 15 mg P bis 600 mg P einer Diphosphonsäureverbindung nach einem der Ansprüche 1 bis 3; und
   b) einen pharmazeutischen Träger.

Revendications

1. Acide cycloalkyldiphosphonique géminal ou sel pharmaceutiquement acceptable de celui-ci, choisi parmi :
   (a) les acides dihydro-1-pyrindine-6,6-diphosphoniques substitués ou non substitués; et
   (b) les acides dihydro-2-pyrindine-6,6-diphosphoniques substitués ou non substitués;
   dans lequel les substituants dudit acide cycloalkyldiphosphonique substitué sont choisis parmi les groupes méthyle, méthylamino, amino, chloro, hydroxy et méthoxy.

2. Acide dihydro-1-pyrindine-6,6-diphosphonique ou sel pharmaceutiquement acceptable de celui-ci.

3. Acide dihydro-2-pyrindine-6,6-diphosphonique ou sel pharmaceutiquement acceptable de celui-ci.

4. Composition pharmaceutique, comprenant
   a) de 15 mg de P à 600 mg de P d'un composé acide diphosphonique selon l'une quelconque des revendications 1 à 3; et
   b) un véhicule pharmaceutique.